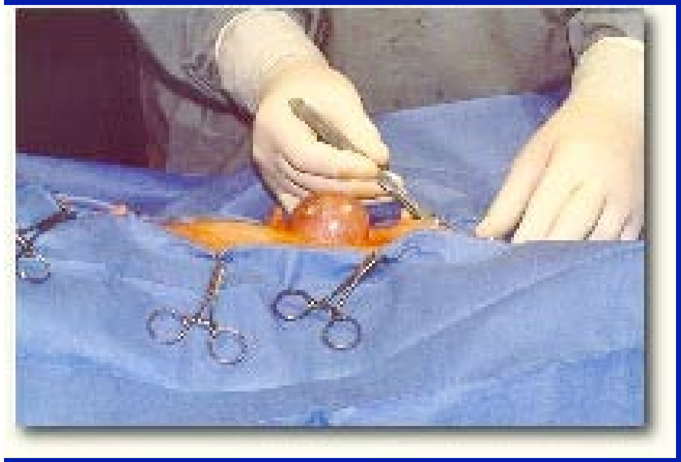
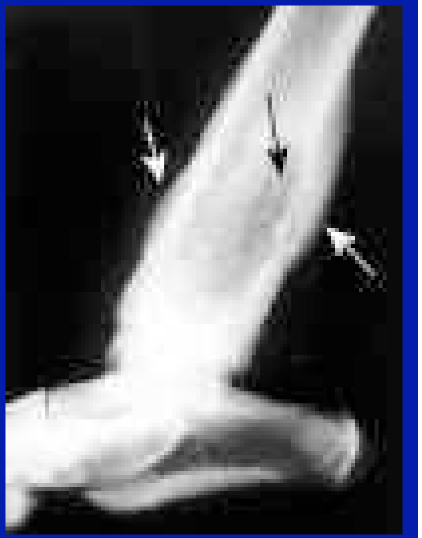
Nociception I
Overview of Pain

International workshop on pain in 2002 concluded that "animals feel pain, but that it is unclear at this time whether all species including humans feel pain with the same qualities and intensities, operationally, all vertebrates and some invertebrates experience pain."





I. Terminology:

A. **Pain—**an unpleasant sensory and emotional experience associated with actual or potential tissue damage. It is a protective mechanism for the body and causes a human or animal to react to remove the pain stimulus. It is a complex sensory experience with many subjective components: 1) discriminative; 2) learning and memory—associate pain with certain events; 3) unpleasantness, displeasure and 4) suffering, escape.

B. **Noxious—**a stimulus that damages or threatens damage to tissue, it can be mechanical, thermal or chemical.

C. **Nociceptor—**a primary afferent neuron that is preferentially sensitive to a noxious stimulus.

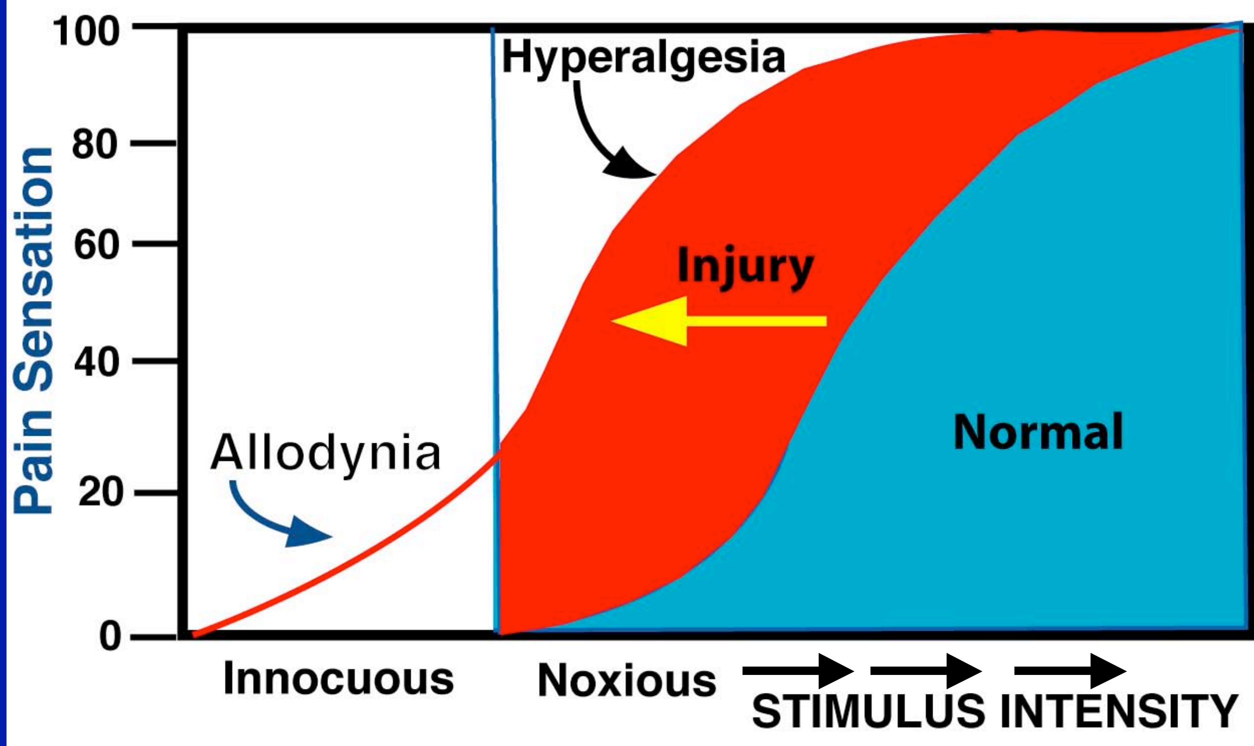
D. **Nociception—**the detection of tissue damage by specialized transducers (nociceptors) attached to "A delta" and "C" peripheral nerve fibers. The term "Nociception" is often used interchangably with the term "Pain", but technically refers to the transmission of nociceptive information to the brain without reference to the production of emotional or other types of response to the noxious stimulus.

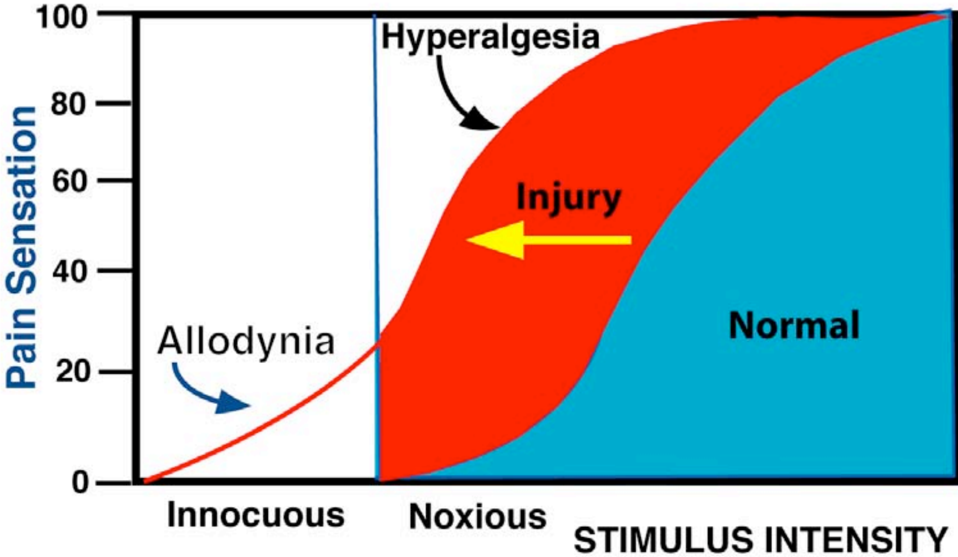
E. Algesic—pain producing vs. **Analgesic—**pain preventing

F. Hyperalgesia—increased pain sensation elicited by a noxious stimulus

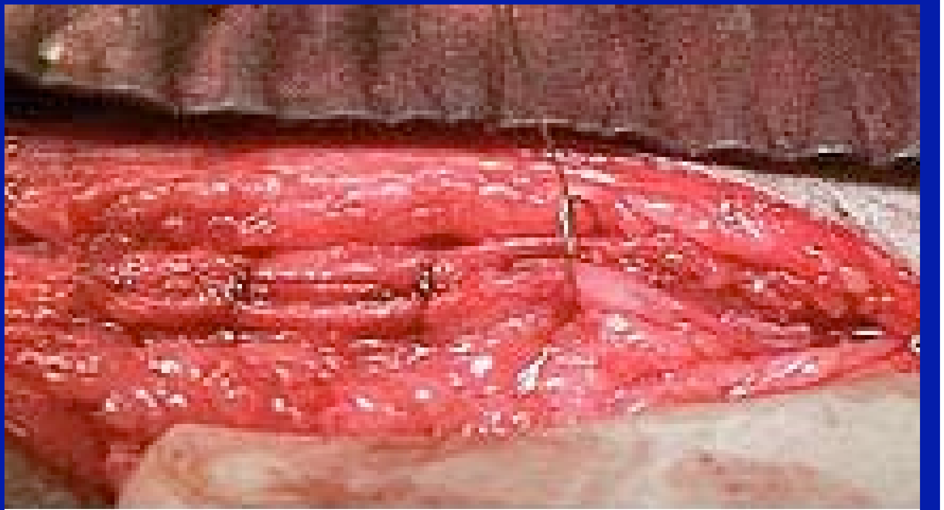
G. Allodynia—a pathological condition in which pain is produced by a stimulus that is normally innocuous (sunburn).

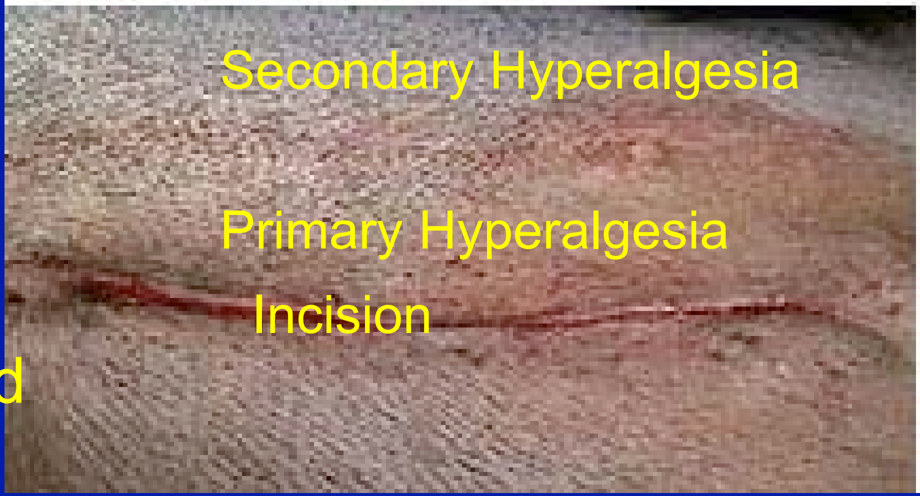
Graph showing normal pain sensation (blue); hyperalgesia (red) & allodynia





Abdominal Incision Dog/Spay

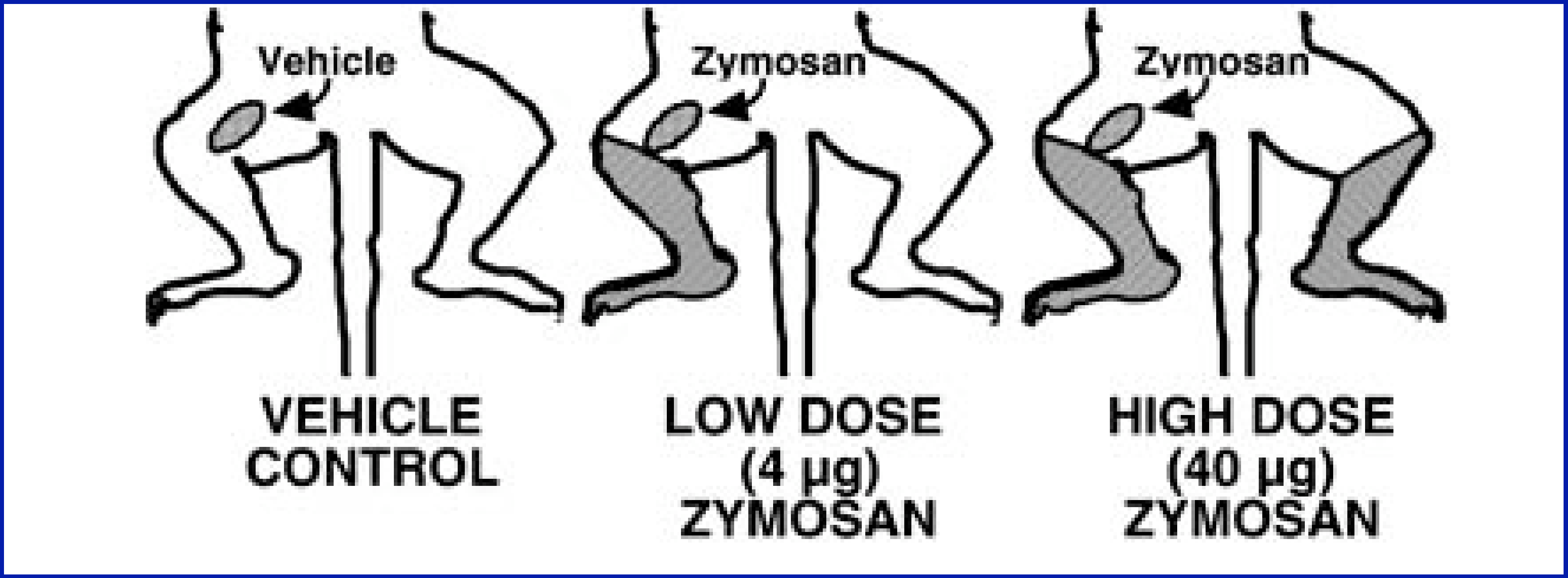




Primary hyperalgesia-increased pain sensation at the site of injury

Secondary hyperalgesia-increased pain sensation distant from the site of injury.

Hindlimb hyperalgesia produced by delivery of an immunogenic stimulus delivered around the sciatic nerve at mid-thigh level (sciatic inflammatory neuropathy model)



No hyperalgesia

Unilateral hyperalgesia

Bilateral Hyperalgesia due to spinal cord sensitization

II. How to Recognize Pain in Animals:

1) Is there situational evidence that pain exists: recent injury?

2) Are there altered behavioral responses—increased aggressiveness, avoidance behavior, reluctance to be touched, decreased appetite, lethargy, vocalization, crying, yelping, lameness?

A cat in pain after surgery is hunched, immobile and unresponsive

3) Are there physiological changes, altered autonomic function, increased heart rate or blood pressure, increased respiratory rate (hyperventilation) increased sweating, salivation?

4) Are there biochemical changes—increases in cortisol or adrenaline in the blood?

Signs of pain in dogs (n=231) and cats (n=92) examined as outpatients at the Ohio State University during 2002

Signs of Pain	No. of Dogs (%)	No. of Cats (%)
Lameness	96 (42%)	20 (22%)
Behavioral Signs		
Change in behavior	50 (22%)	27 (29%)
Anxiousness	18 (8%)	1 (1%)
Signs of depression	10 (4%)	4 (4%)
Aggression	4 (2%)	0 (0%)
Vocalizing	14 (6%)	11 (12%)
Signs of Pain with palpation	29 (13%)	25 (27%)

And now for something completely different!

III. Pain Transmission and Pain Pathways

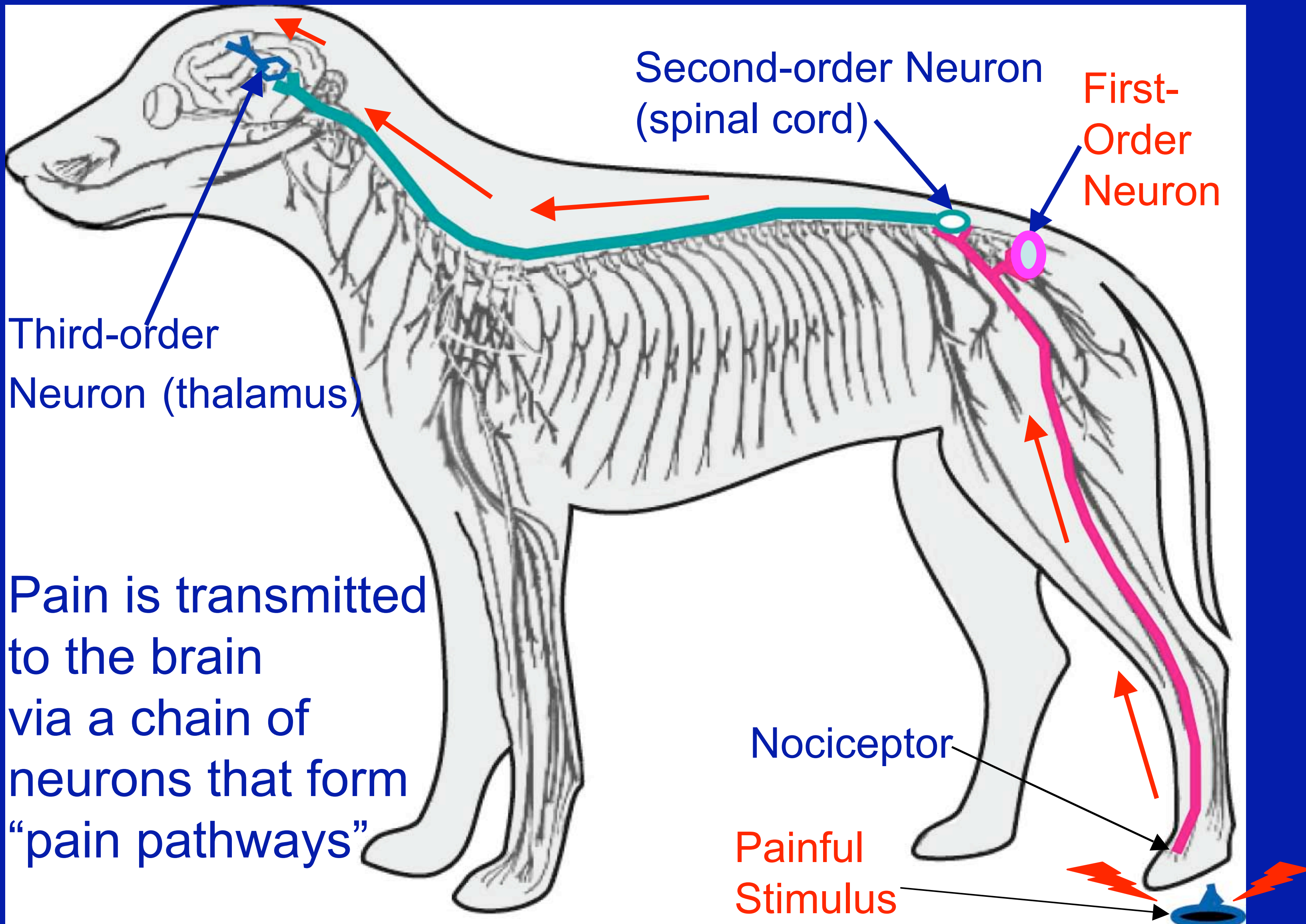
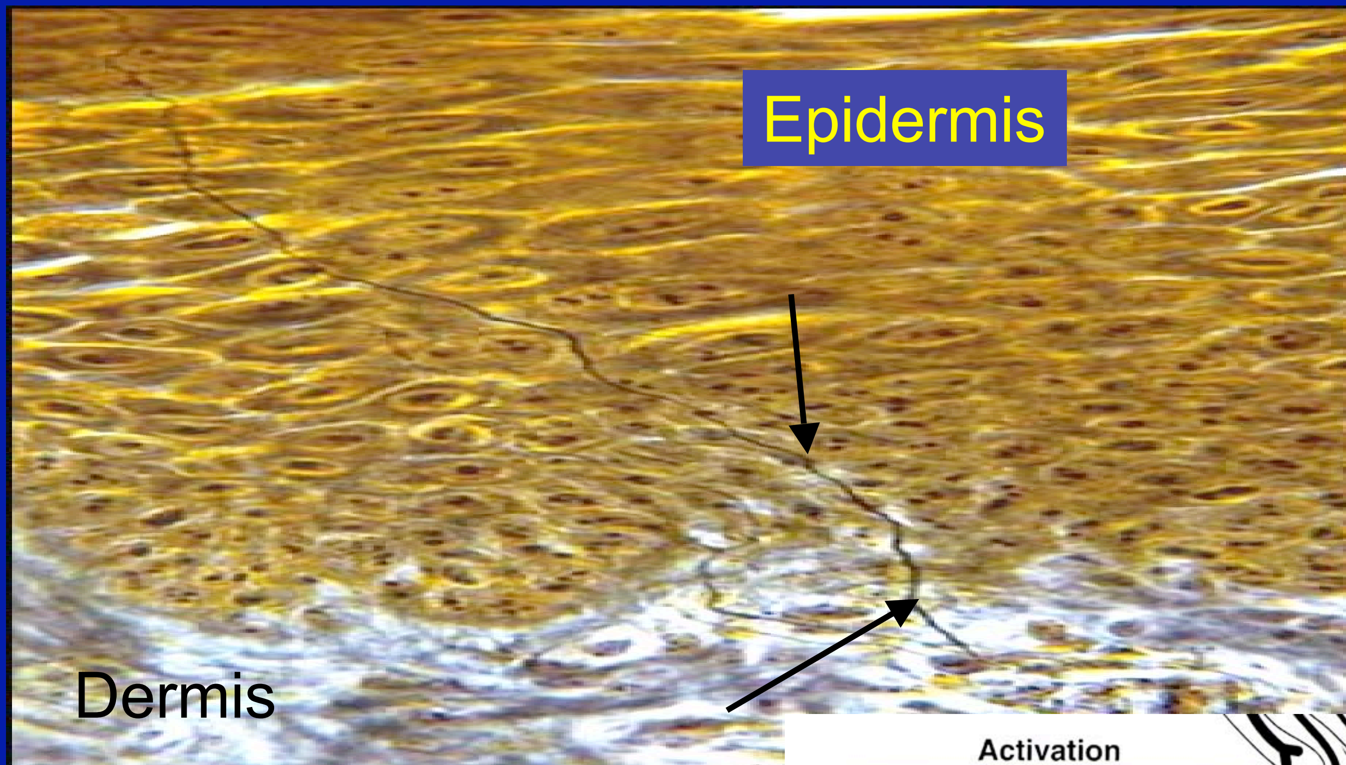


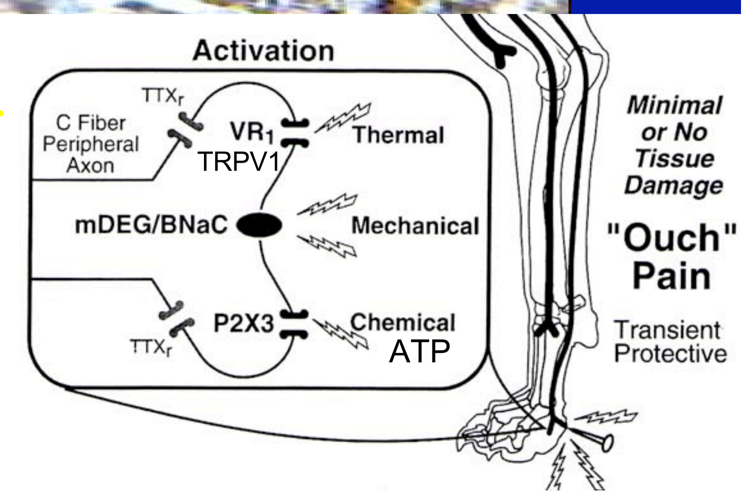
Fig. 2: Schematic overview of the 3-neuron spinothalamic pathway

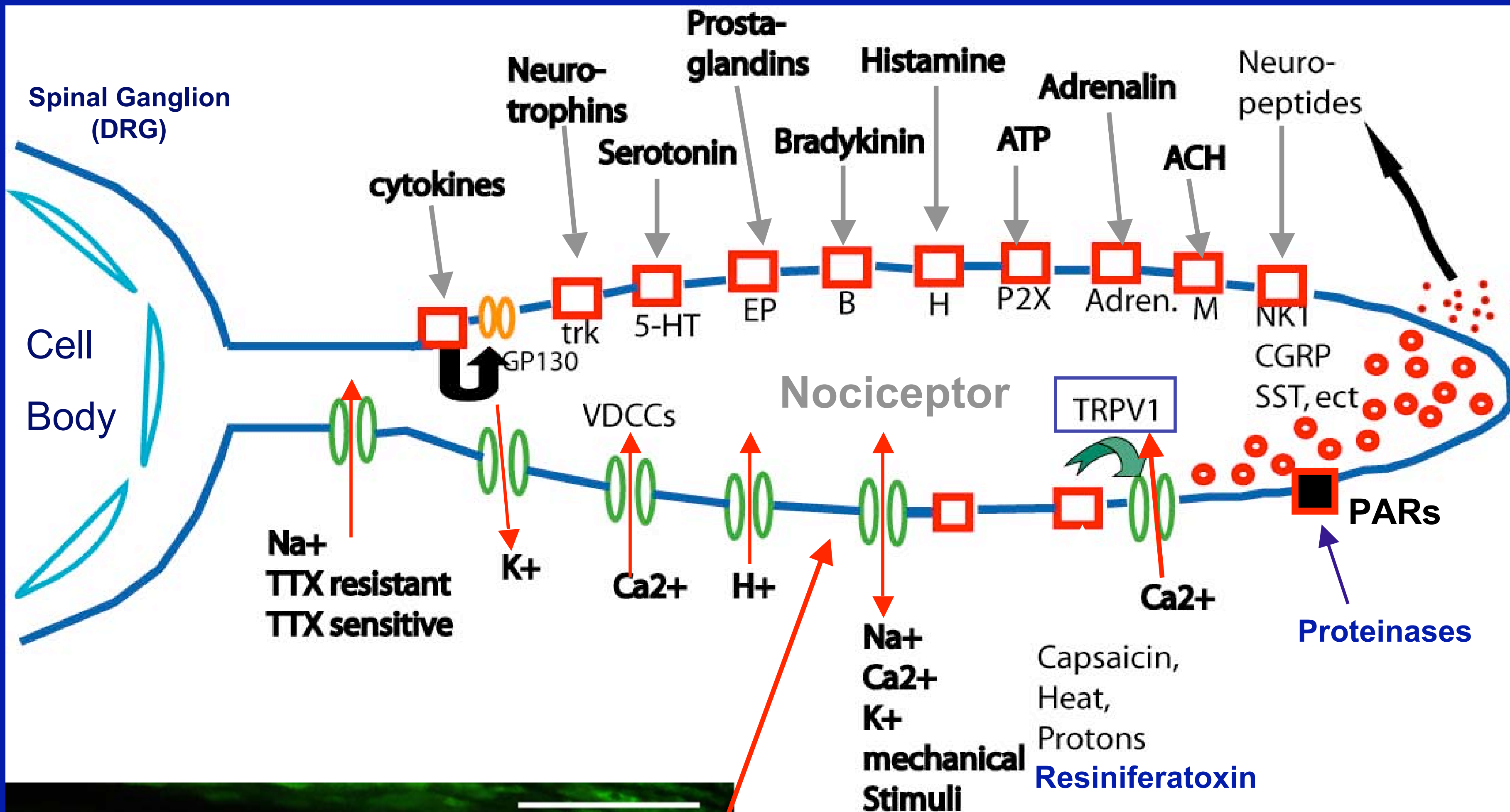
A. Peripheral Transmission: Pain or nociception is initiated when peripheral nerve terminals (receptors) of a subgroup of sensory neurons (nociceptors) are activated by noxious chemical, mechanical or thermal stimuli.



Skin

1. Receptors — **free nerve endings** (non-myelinated terminals which contain synaptic vesicles). Damage to tissue causes the release of a number of mediators that activate nociceptor free nerve endings. These mediators include ATP from damaged cells and bradykinin from blood (Fig. 2). In response to activation these terminals may actually release their transmitters (substance P, CGRP and other peptides) into the extracellular fluid in the area that they are located, this amplifies the pain sensation.





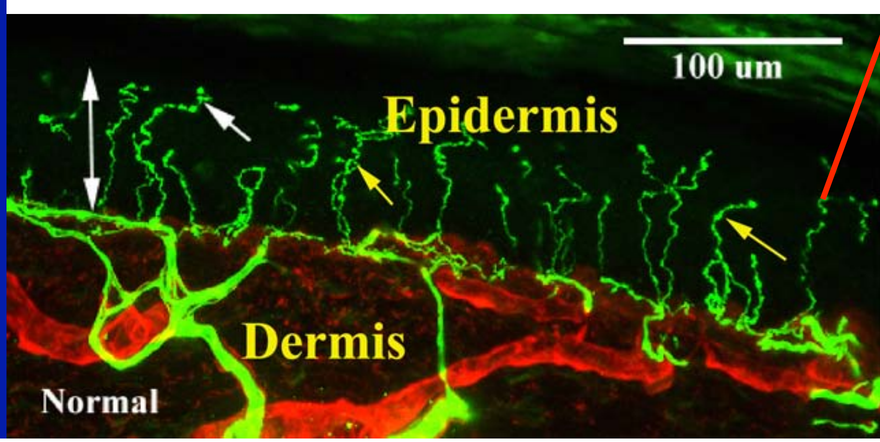


Fig. 3: Influence of inflammatory mediators upon the activity of a **"c-fiber" nociceptor** following injury.

2. Peripheral nociceptors have their cell body or soma in a spinal or cranial nerve ganglia. The cell body gives rise to: 1) a peripheral process or primary afferent axon that innervates skin, muscle, viscera, etc. as a free nerve ending and 2) a central process that terminates in the spinal cord dorsal horn or in the brain stem.

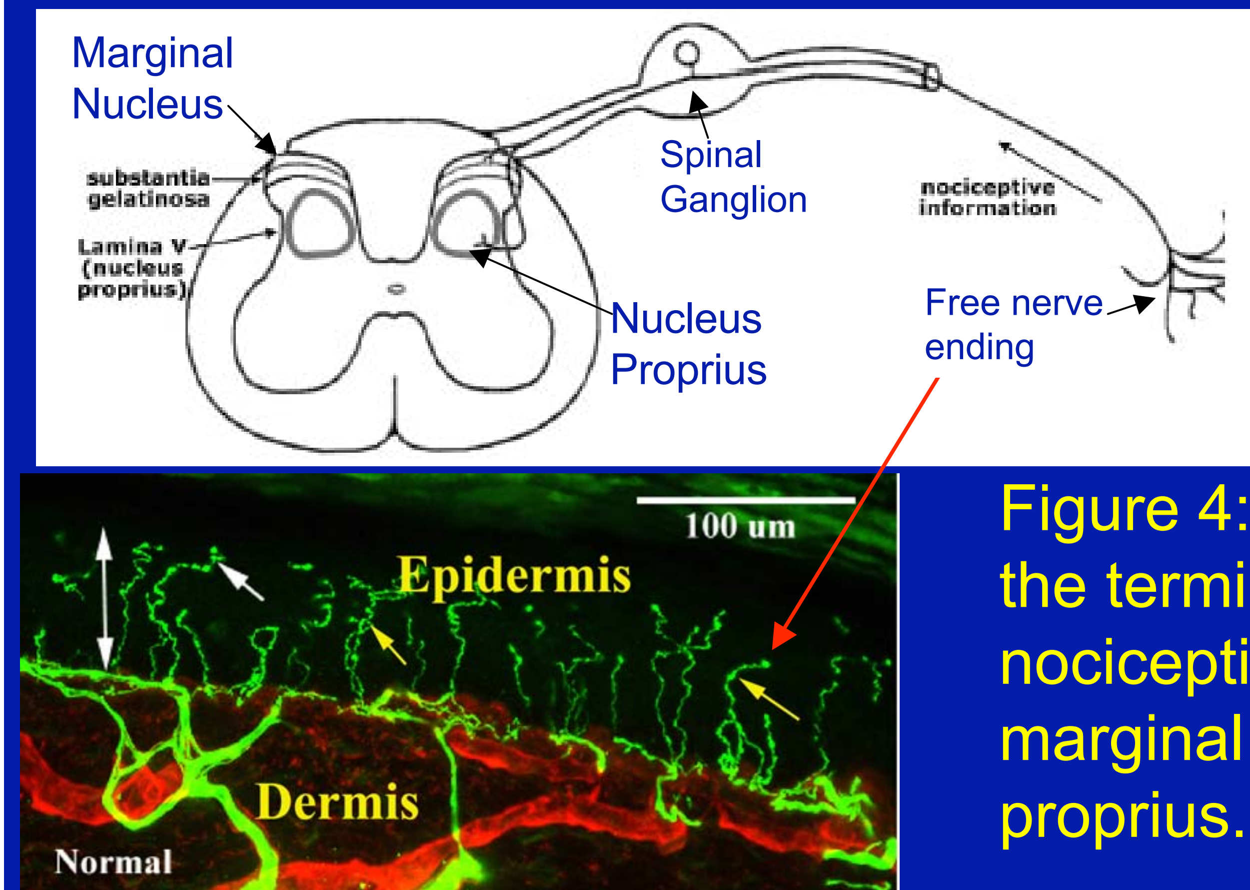
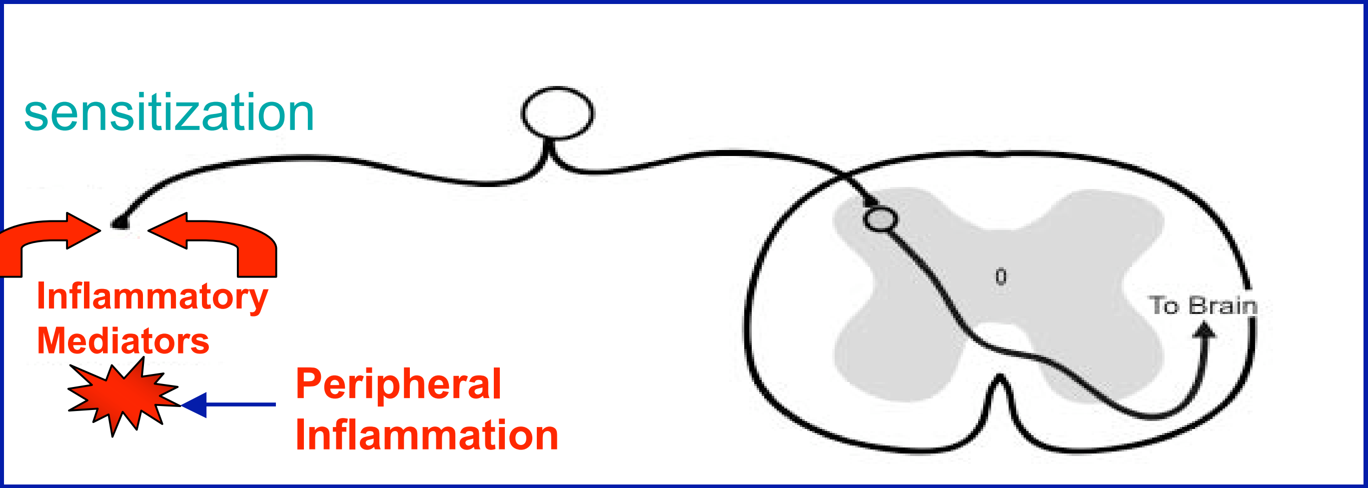


Figure 4: Diagram illustrating the termination sites of nociceptive fibers in the marginal nucleus and nucleus proprius.

Pain Sensitivity: Pain receptors become sensitized after tissue damage. When tissue is damaged or a noxious stimulus is repeated nociceptors exhibit sensitization in that there can be a reduction in the threshold for activation, an increase in response to a given stimulus, or the appearance of spontaneous activity. This sensitization results from the actions of second messenger systems activated by the release of inflammatory mediators (bradykinin, histamine, prostaglandins, serotonin) at the site of injury. This causes some of the features of **hyperalgesia** produced by tissue damage or by pathological processes.



3. Noxious information is transmitted from nociceptive receptors by 2 types of axons:

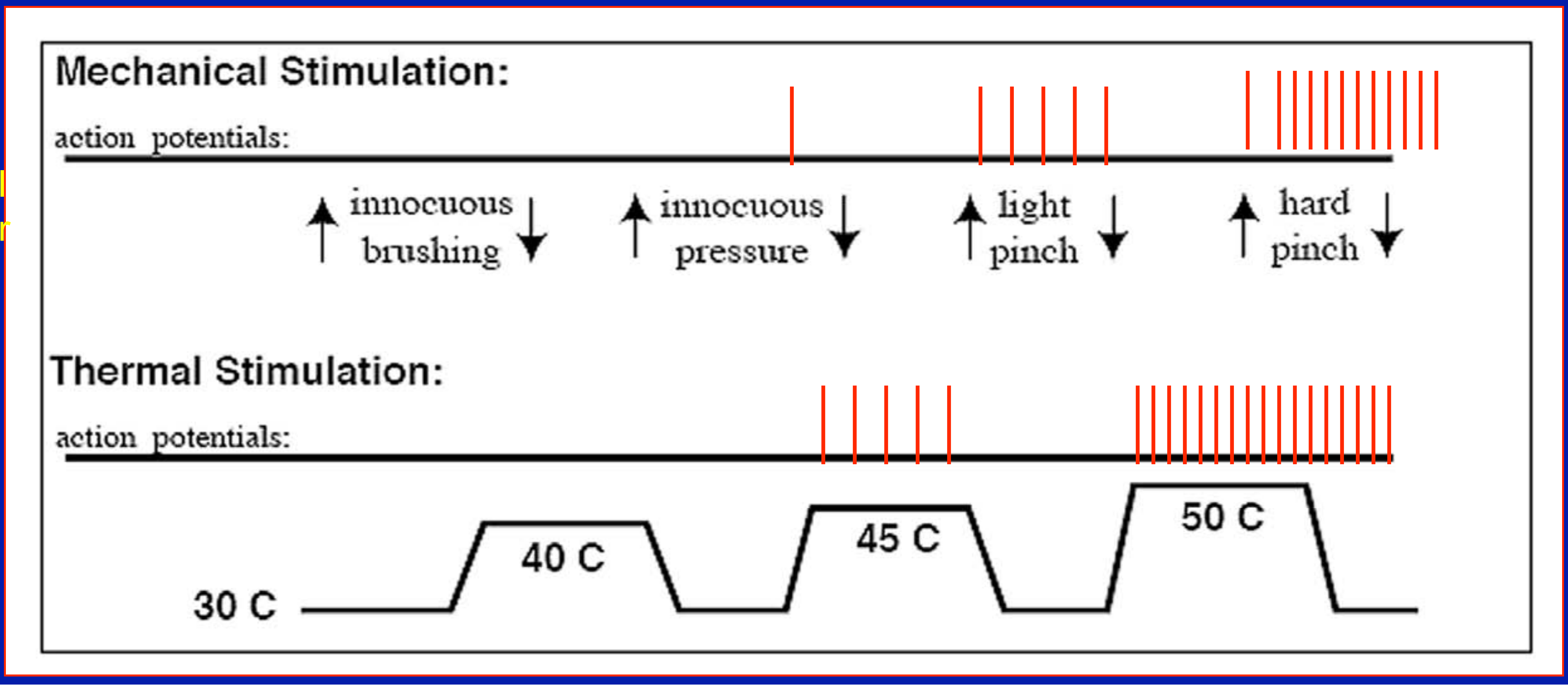
(1) A-delta fibers—lightly myelinated, conduct at velocities of 2-30 M/sec (1st pain)

(2) C-fibers—unmyelinated, conduct at velocities of less than 2 M/sec (2nd pain).

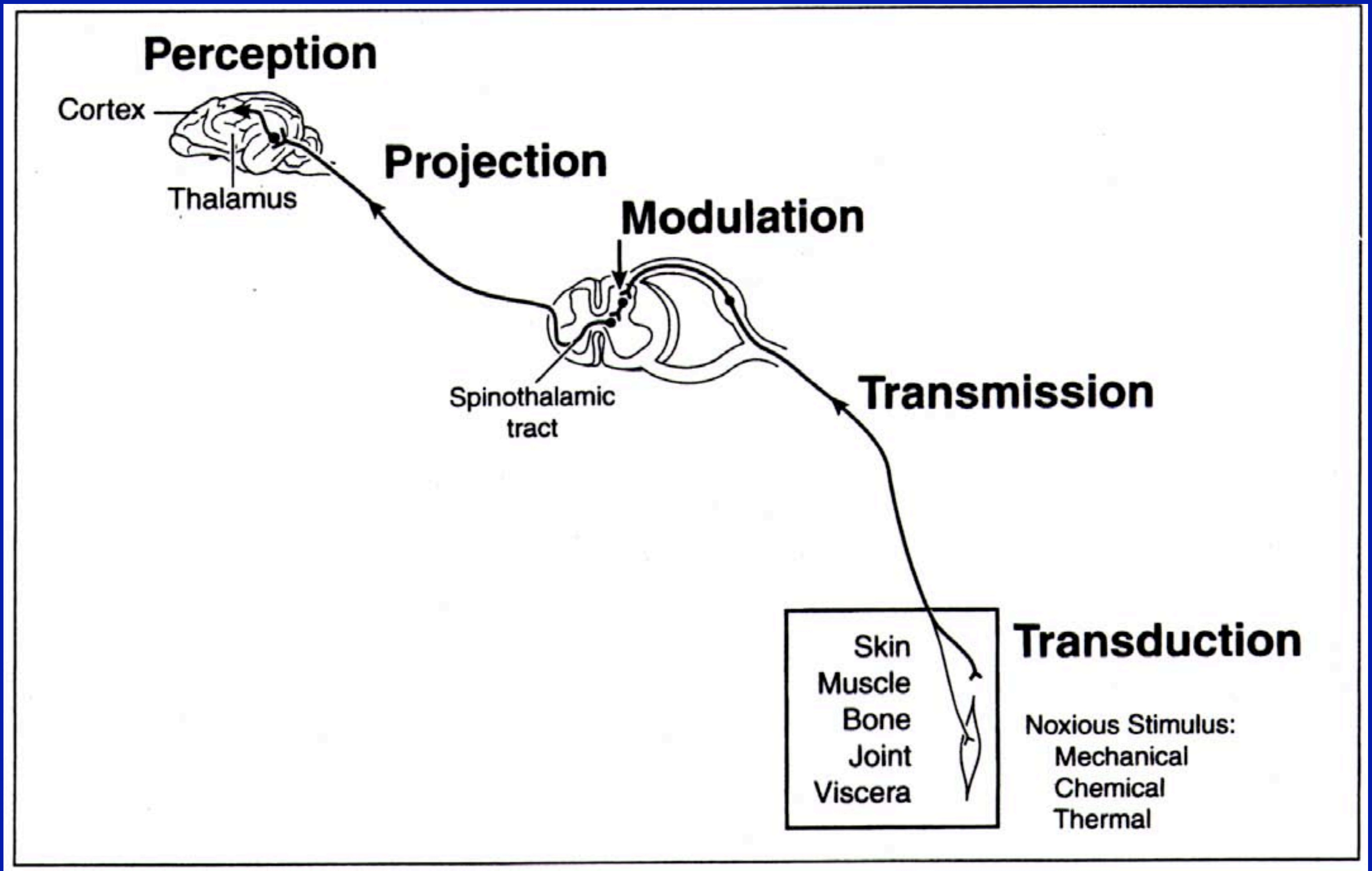
NOTE: A δ and C fibers can be classified into various types based on their functional properties. For example C fibers can be divided into: C-mechanical/heat nociceptors; C Polymodal Nociceptors (sensitive to heat, mechanical & chemicals) and Cold Nociceptors.

4. Primary Response Characteristics (action potential frequency codes stimulus intensity

Polymodal Nociceptor

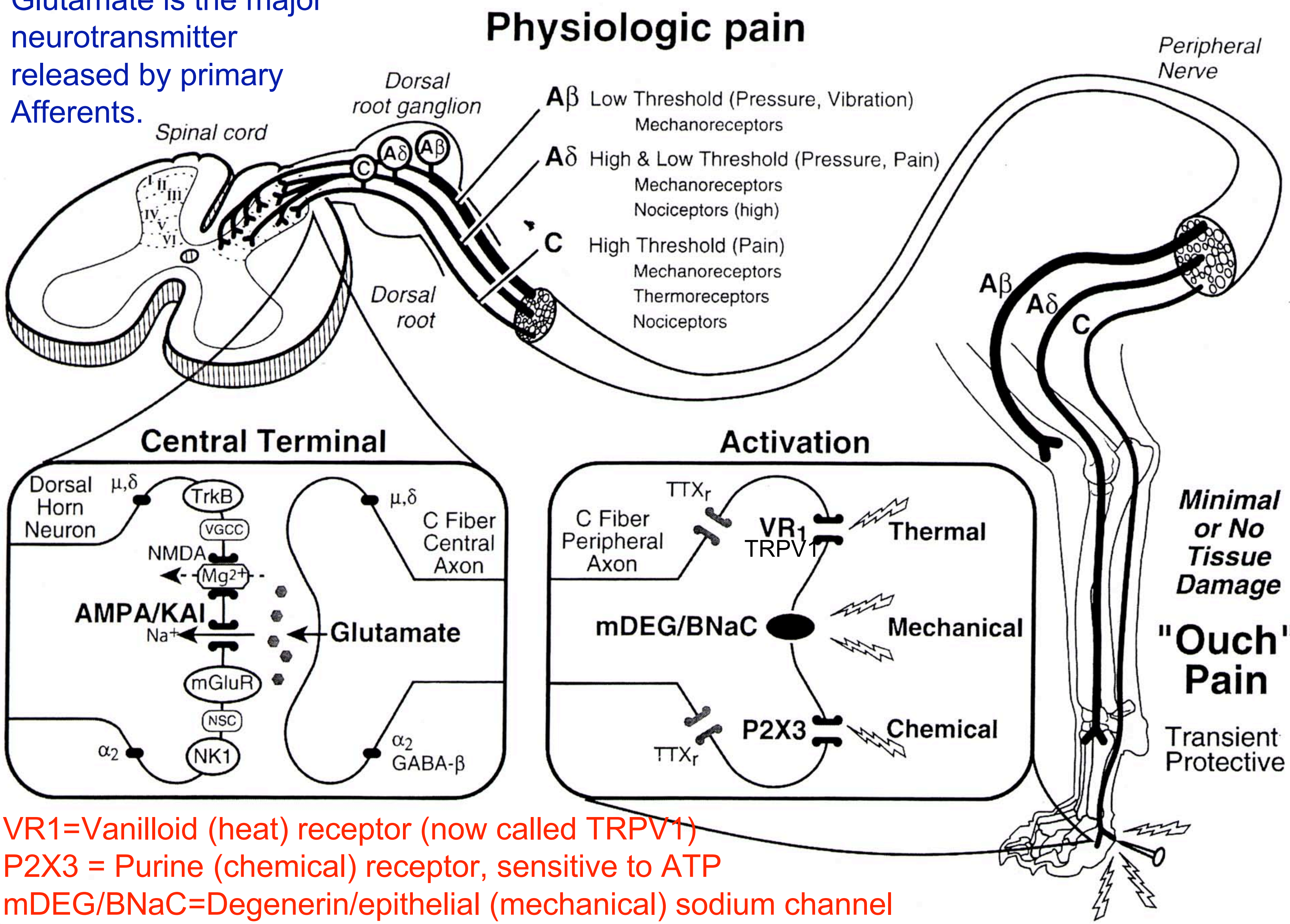


B. Central Transmission: Pain is transmitted from Primary Afferent Axons (axons from cell bodies in a spinal ganglion)→ the spinal cord dorsal horn (marginal nucleus or nucleus Proprius)→ thalamus→cerebral cortex.



Structures involved in normal "physiological" pain

Glutamate is the major neurotransmitter released by primary Afferents.



VR1=Vanilloid (heat) receptor (now called TRPV1)

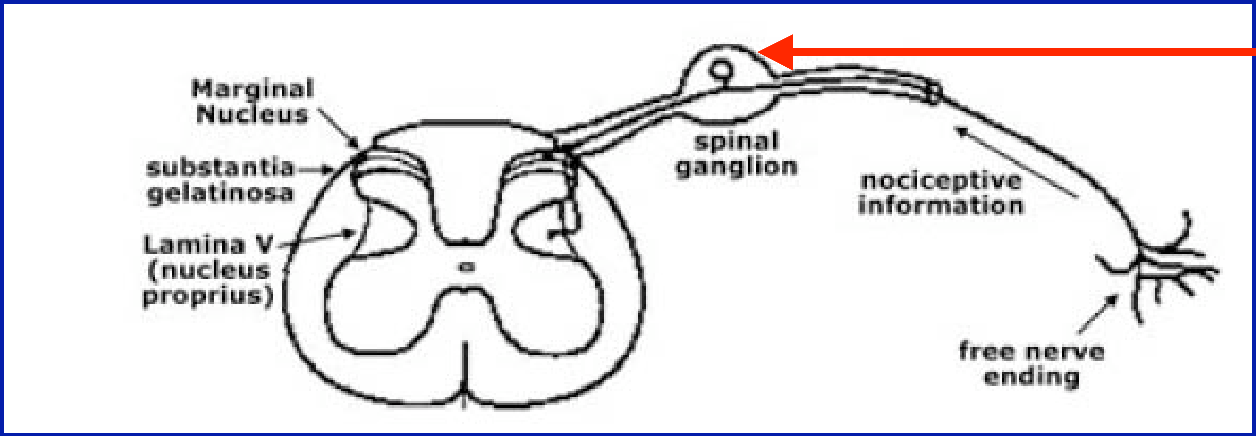
P2X3 = Purine (chemical) receptor, sensitive to ATP

mDEG/BNaC=Degenerin/epithelial (mechanical) sodium channel

Pain sensation is conveyed from the spinal cord by several central nervous system pathways, the two most important in animals are: (1) the **Spinothalamic pathway** and (2) the **Spinocervicothalamic pathway.**

1. The Spinothalamic Pathway: this pathway is classically considered to be the major pain relay system in mammals. Although this pathway clearly plays an important role in carnivores the spinocervicothalamic pathway plays an equally important role in pain transmission in dogs and cats. The organization of the spinothalamic pathway can be summarized as follows:

(A) 1st order Neuron: Cell body located in a spinal (dorsal root) ganglion, Its peripheral process is associated with the receptor, while its central process enters the gray matter of the spinal cord to synapse in the **Marginal Nucleus Substantia gelatinosa (lamina II) and Nucleus proprius.**

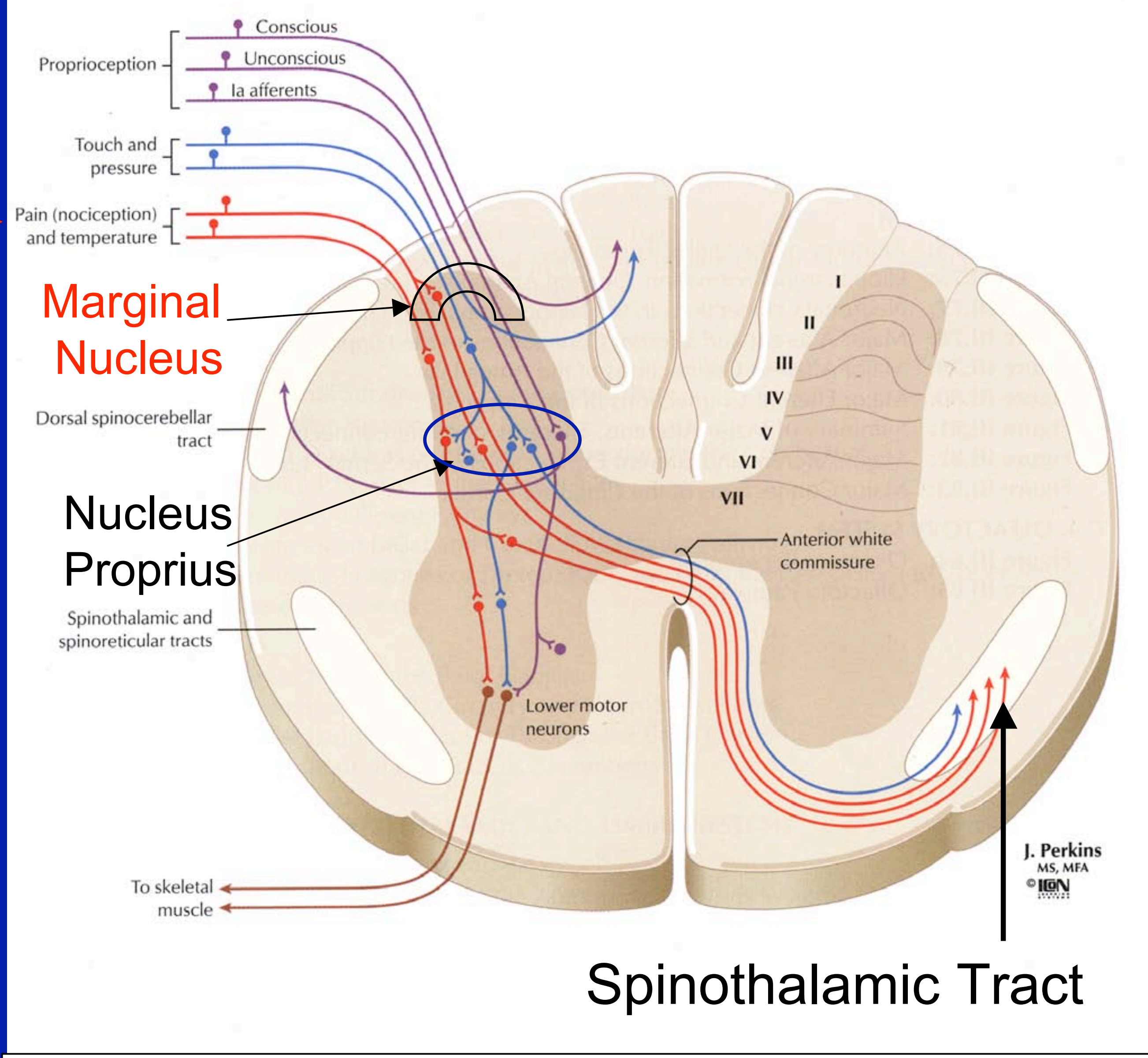


1st Order Neuron

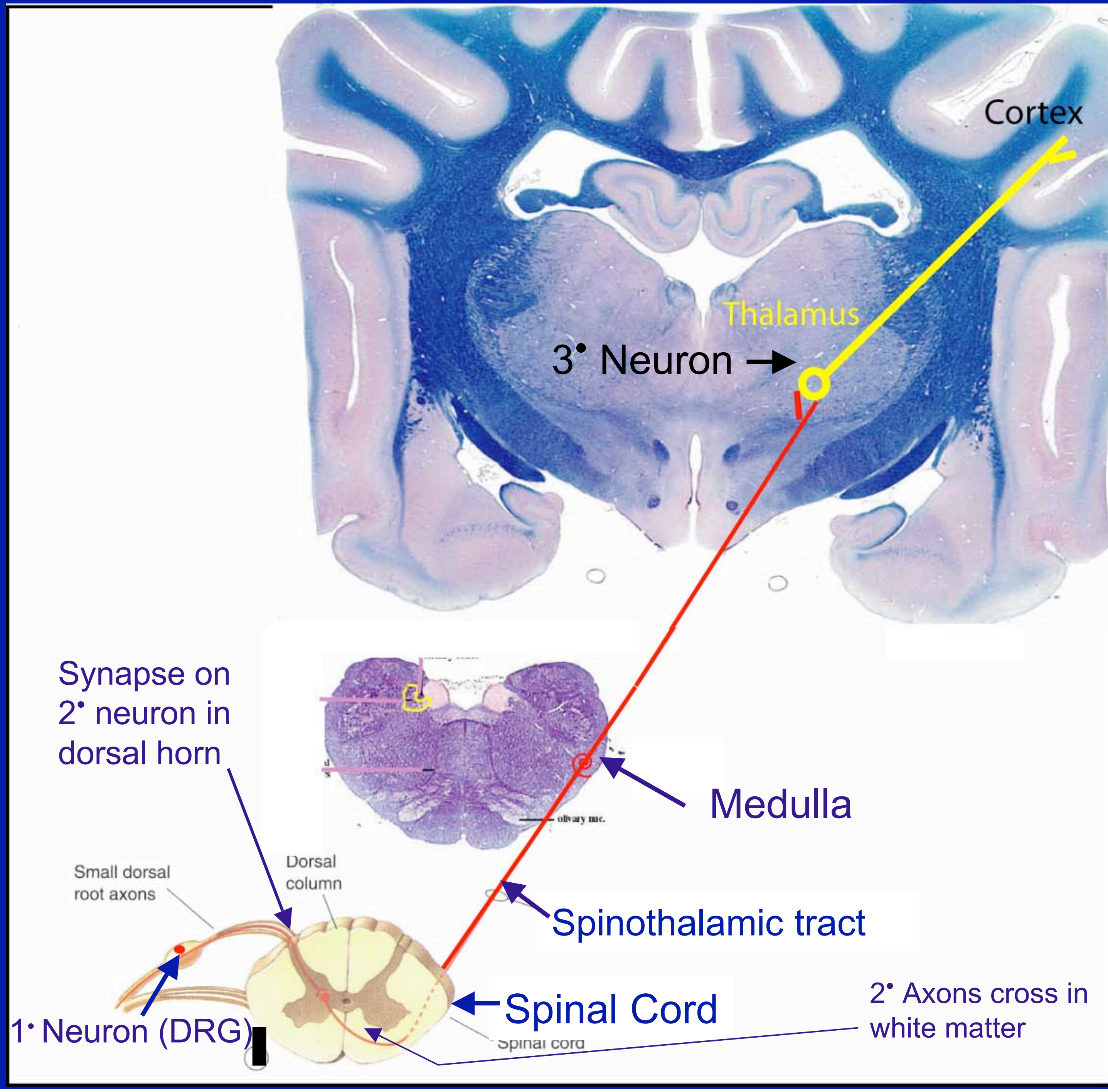
Transmitters: Glutamate & aspartate; substance P, somatostatin

Pain Input

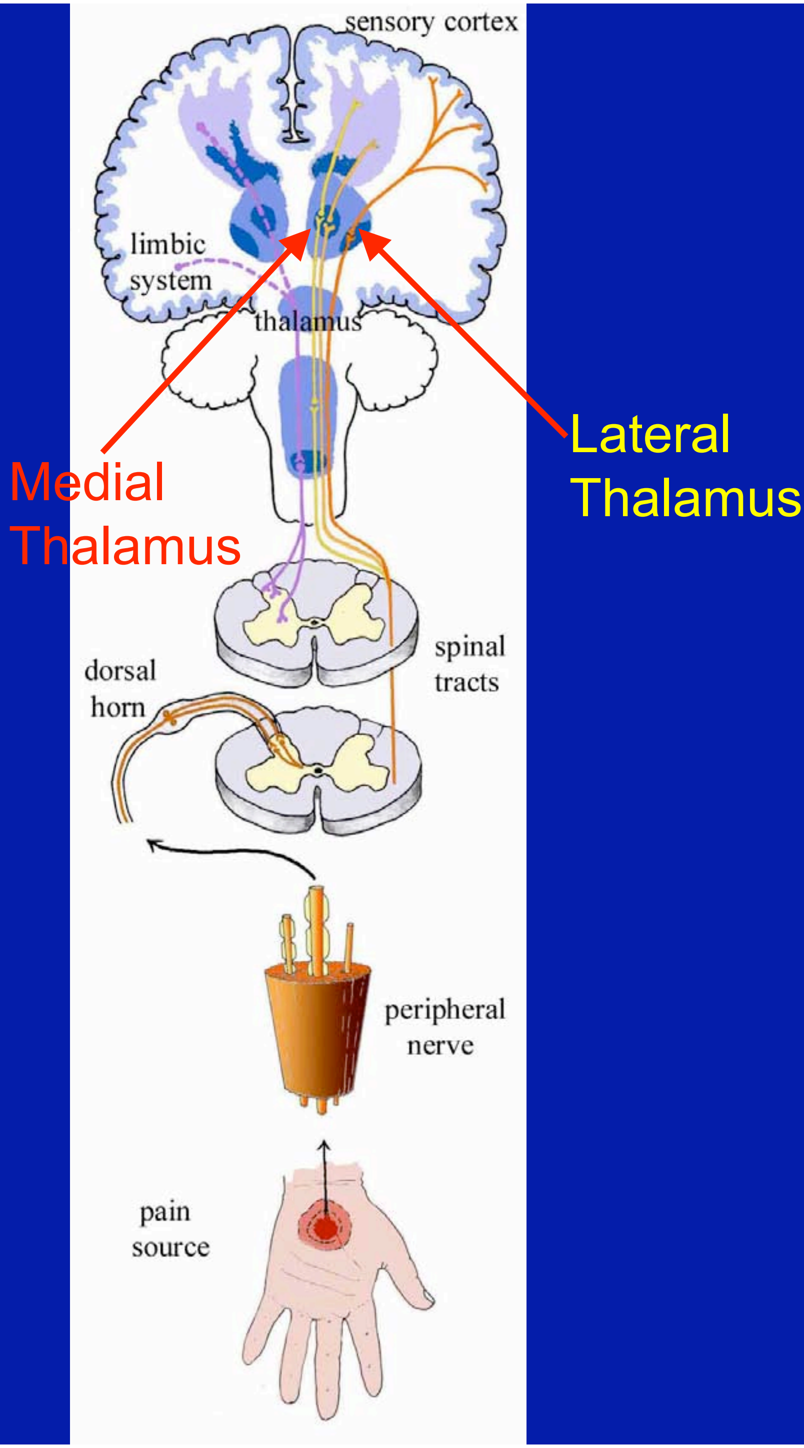
(B). Second order Neuron: cell bodies located in the **marginal nucleus** and the **nucleus proprius.** Axons of second order neurons cross the midline and join other axons which also carry pain sensation. These axons form the **Spino-thalamic tract** (see fig. 7). Axons travel to→**Thalamus**



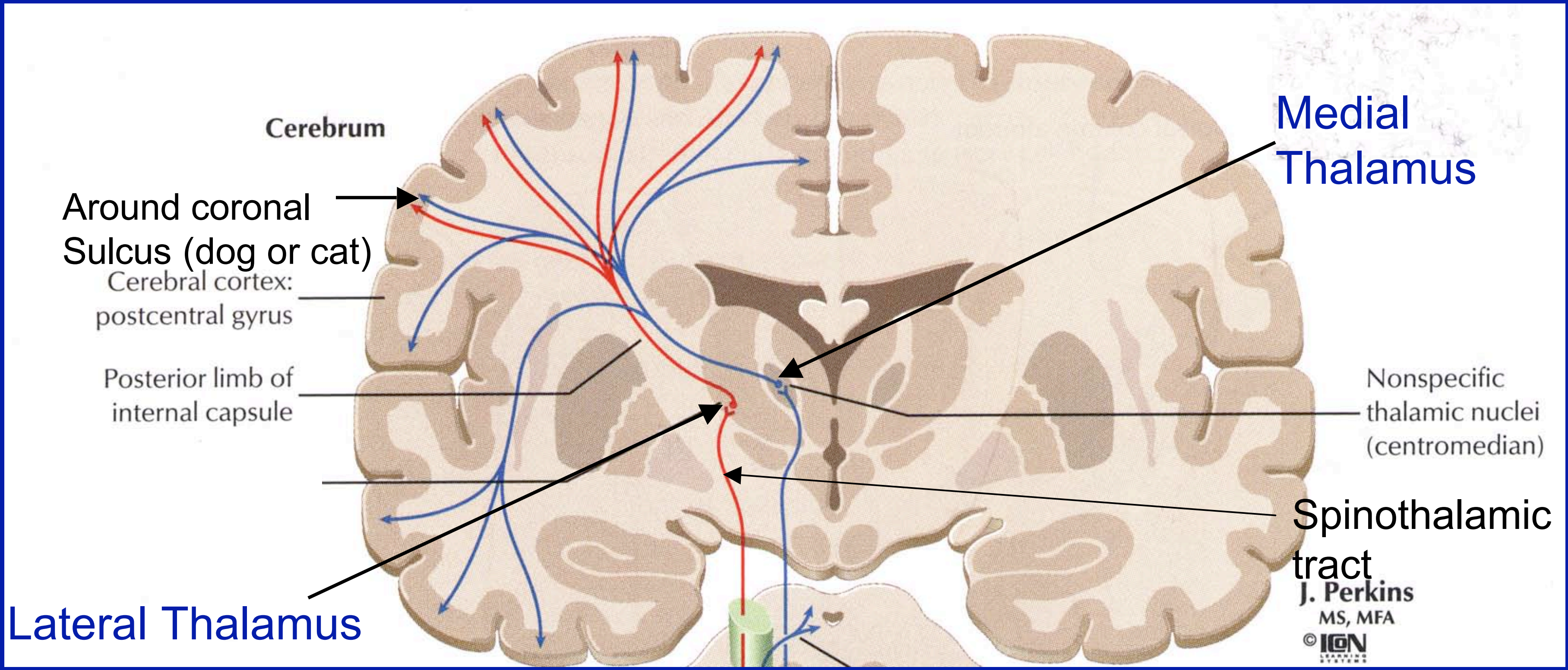
Pain Pathways: Spino-thalamic tract



(C). The axons of 2nd order neurons synapse on 3rd order neurons in the thalamus. The **Thalamus** is the crucial relay for the reception and processing of nociceptive information in route to the cortex. Axons terminating in the **lateral thalamus** mediate discriminative aspects of pain. Axons terminating in the **medial thalamus** mediate the motivational-affective aspects of pain (emotional aspects of pain; attention to and memory of pain).

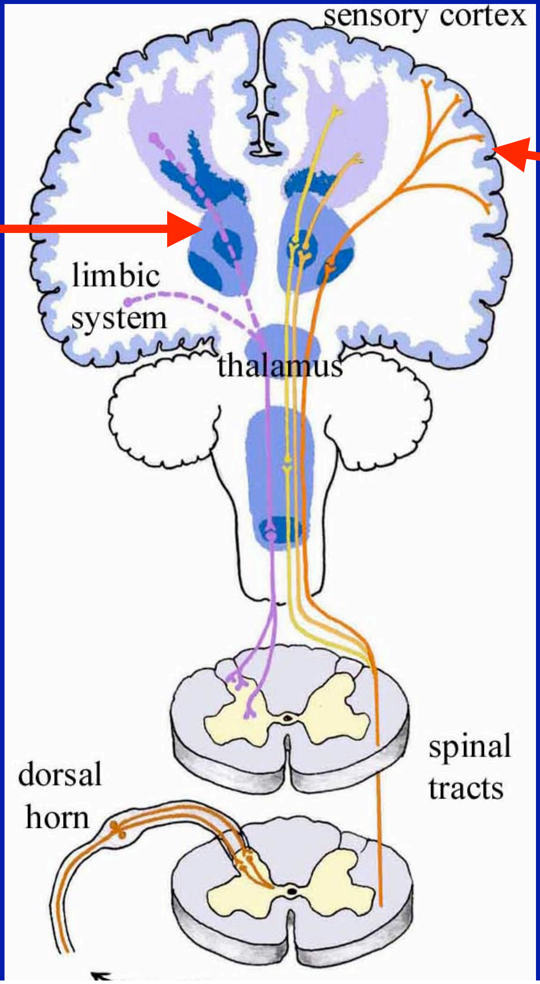


(D) These 3rd order neurons in the thalamus in turn send their axons to the **cerebral cortex.** Note: neurons in the lateral thalamus (for discrimination) project to the somatosensory cortex. Neurons in the medial thalamus (for affective aspects of pain project to other areas of cortex (prefrontal, insular and cingulate gyrus).



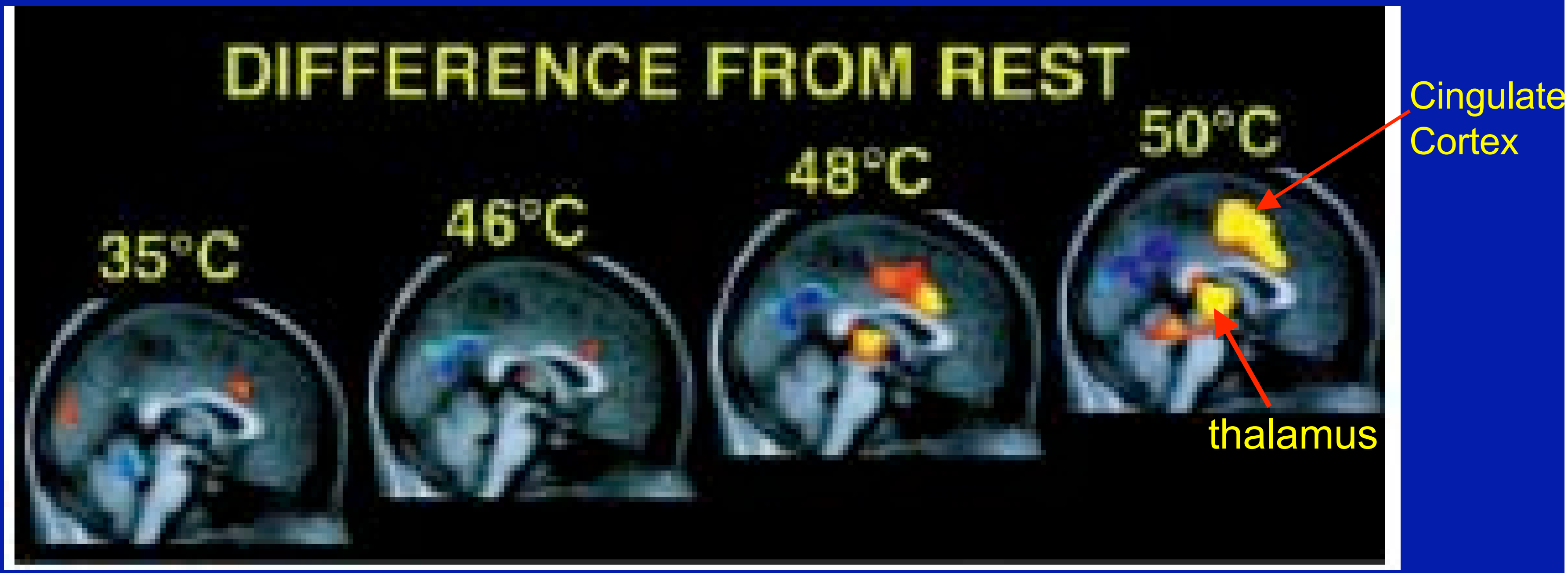
Note: An animal becomes aware of painful stimuli at the level of the thalamus, the cerebral cortex is required for localization of the pain to a specific body region. It should also be noted that in addition to pain the spinothalamic pathway conveys temperature sensation.

Thalamus: Aware of pain



Somatosensory Cortex: required for localization of pain.

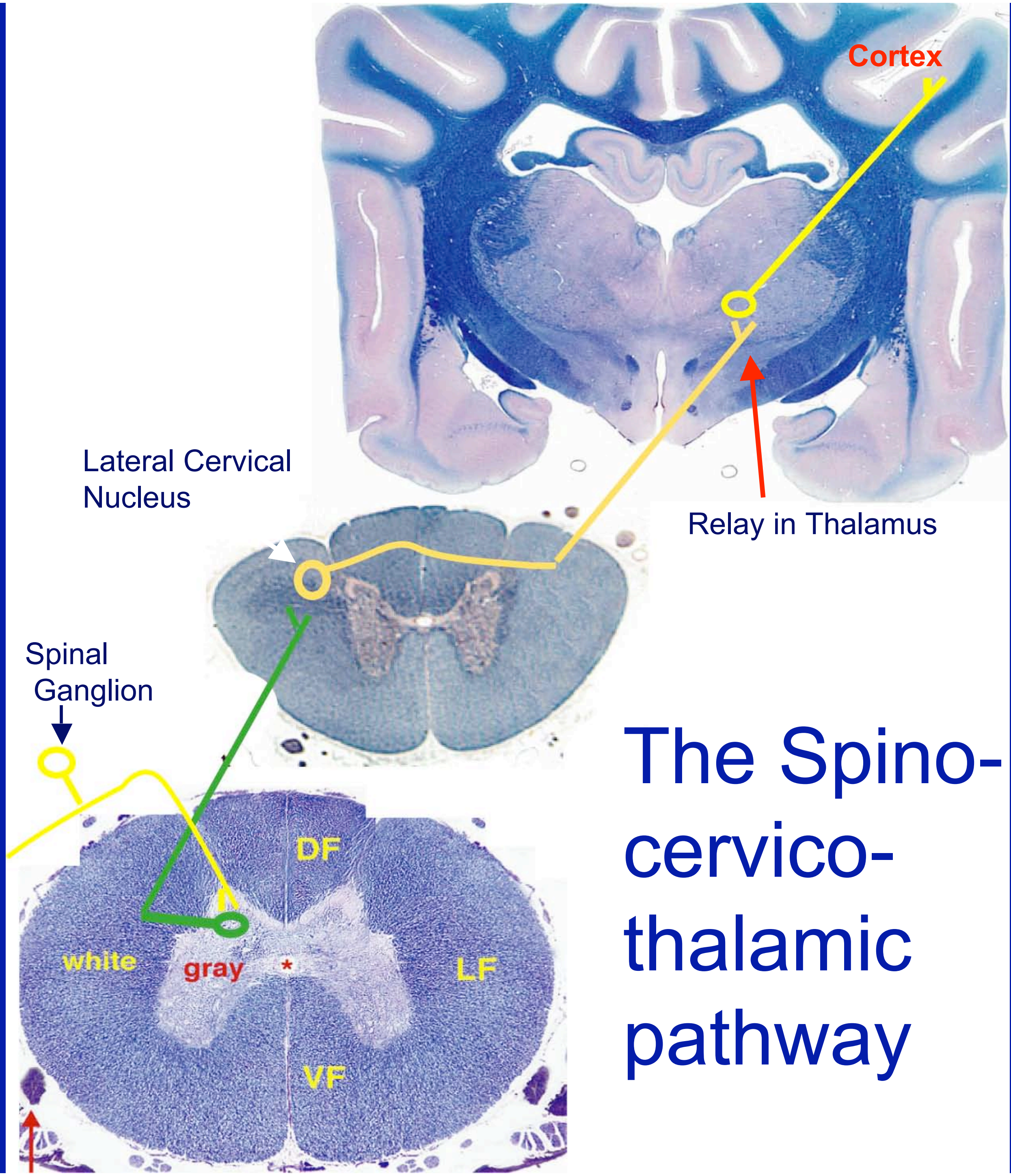
Human brain activity related to pain intensity during acute unilateral noxious heat stimulation. Increases in cerebral blood flow are found in the **thalamus and anterior cingulate cortex** as stimulus temperature increases.



2. Spino-cervico-thalamic Tract: Important in cats and dogs.

A. Receptors: Free Nerve Endings

B. First Order Neurons: Spinal Ganglion



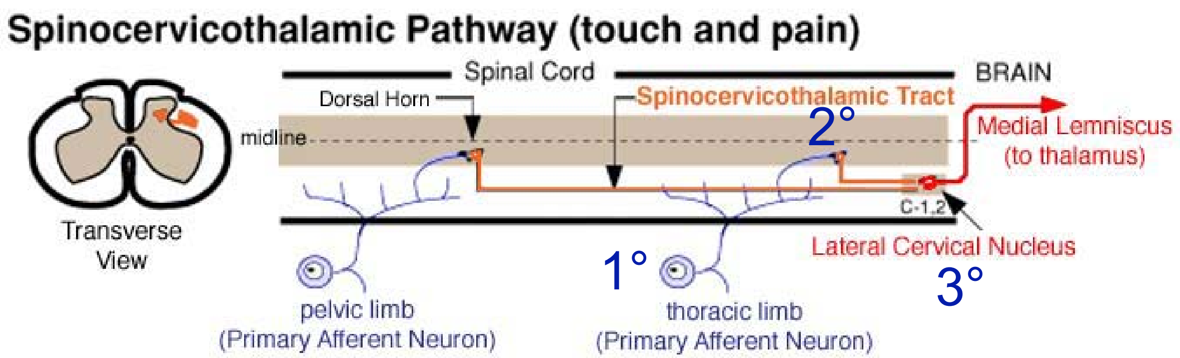
The Spino-cervico-thalamic pathway

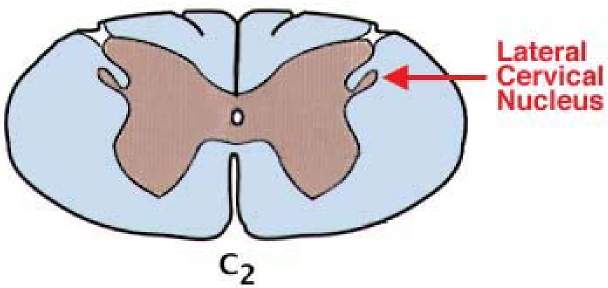
C. 2nd Order neurons: Marginal Nucleus or Nucleus Proprius

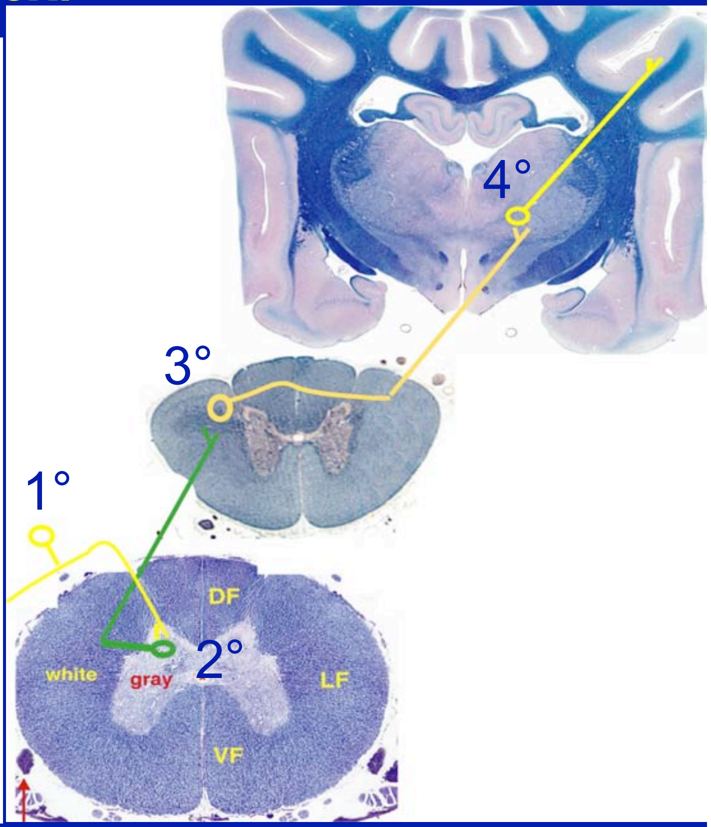
D. Axons of these 2nd order neurons ascend ipsilaterally to the upper cervical spinal cord to synapse on 3rd order neurons located in the Lateral Cervical Nucleus (see fig 1 below)

E. Axons from 3rd order neurons in the lateral cervical nucleus cross the midline and ascend to the contralateral thalamus where they terminate on 4th order neurons.

F. The axons of these 4th order neurons project to the somatosensory area of the cerebral cortex.

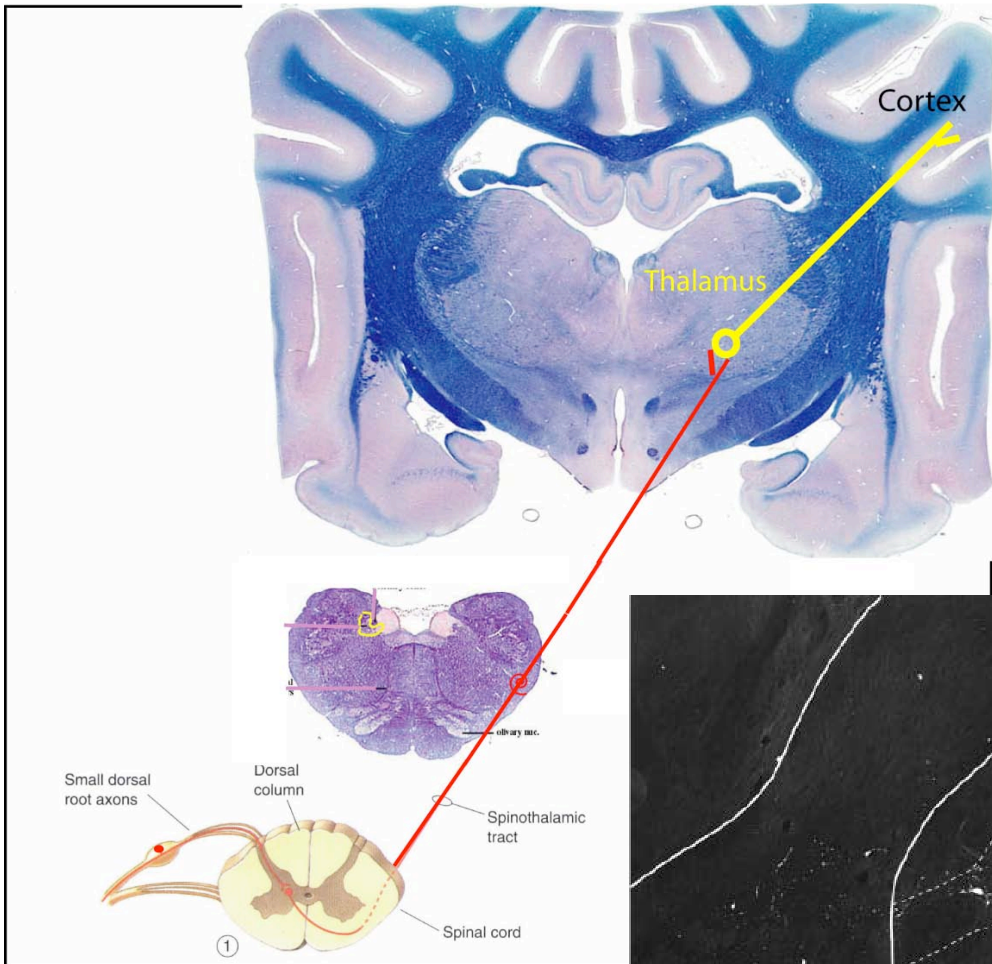






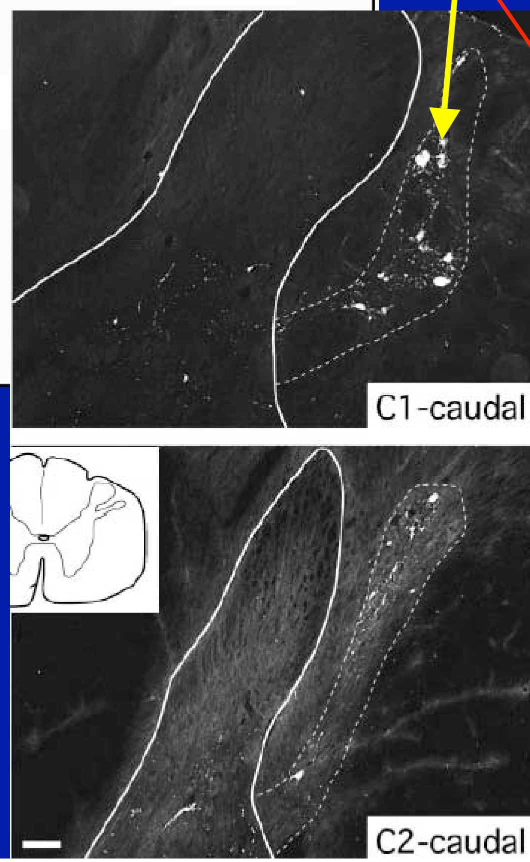
← Spinothalamic Tract

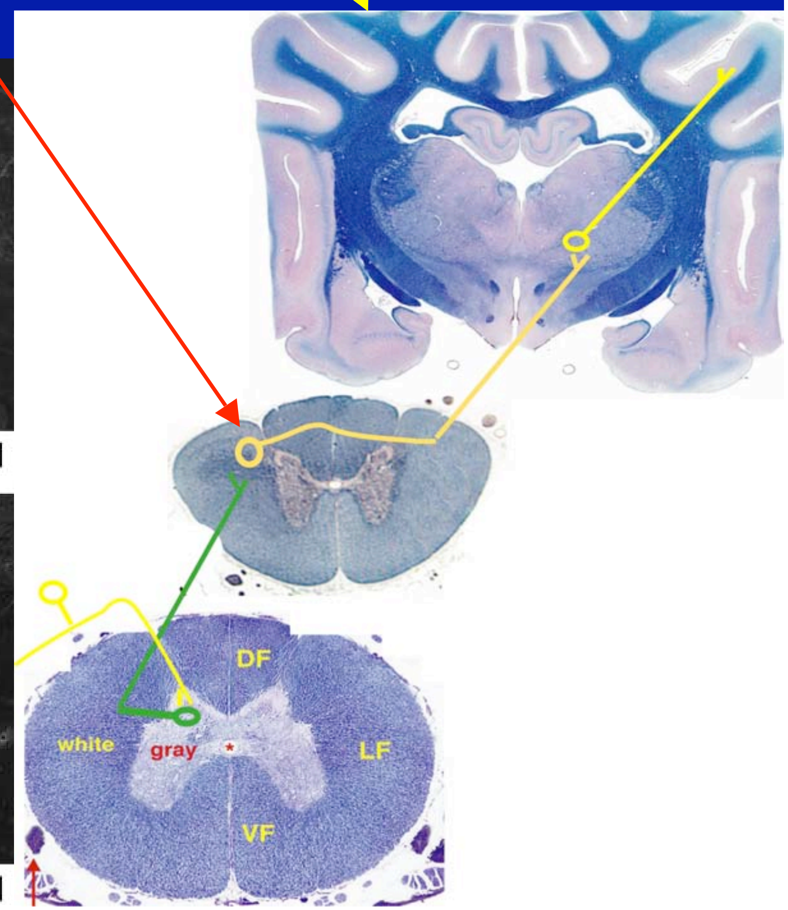
Note: Major difference between the two is the presence of an additional neuron (located in the lateral cervical nucleus) in the pathway.



Spinocervicothalamic Tract

Lateral Cervical Nucleus





Comparison of the two major pain pathways:

The 2006 Hooters Calendar